表 2 N9741試験の成績(文献17より)

	FOLFOX4	IFL	IROX
症例数	267	264	264
奏効率%	45	31	35
TTP(月)	8.7	6.9	6.5
MST(月)	19.5	15.0	17.4

TTP：無増悪期間　MST：生存期間中央値

表 3 GERCOR 試験の成績(文献18より)

	FOLFOX6	FOLFIRI
症例数	111	109
奏効率%	54	56
PFS(月)	8.0	8.5
MST(月)	20.6	21.5

PFS：無増悪生存期間　MST：生存期間中央値

(19.5ヵ月)においてIFL療法，IROX療法を有意に上回るという結果であった(表2)．米国では，この結果oxaliplatinが大腸癌の一次療法として承認されている．続いて2004年にはTournigandらによりFOLFIRI/FOLFOXをクロスオーバーさせた第III相試験が行われ(GERCOR試験)[18]，それぞれの初回治療法の奏効率(56% vs 54%)，無増悪生存期間(8.5 vs 8.0ヵ月)，および全生存期間(21.5 vs 20.6ヵ月)は同等の結果が得られた(表3)．ここに，切除不能転移性大腸癌の化学療法は20ヵ月超の生存期間中央値が得られる時代に到達した．Grotheyらは主な第III相試験の検討において5-FU/LV，CPT-11，oxaliplatinの3種類の薬剤が全治療期間内に使用された症例の割合と全生存期間が相関することを明らかにしており，この3剤を治療期間中に使い切ることで20ヵ月を超える生存が得られるとしている[19]．FOLFOX療法は現時点では比較試験で検討されているFOLFOX4療法やその5FU+LVの2日間の繰り返し投与を1日に簡便化したFOLFOX6療法[20]やFOLFOX7療法[21]が使用されている．しかしながら，どのレジメンが優れているかについては比較検討がされておらず十分なデータがない．本邦ではその簡便さよりFOLFOX6療法が好まれ，さらに，oxaliplatinの投与量を85 mg/m^{2}に減量したmodified FOLFOX6(mFOLFOX6)療法(表1)の有用性が報告され[22]，当院においても主にこのレジメンを使用している．また，oxaliplatinの神経毒性のためFOLFOXを継続できない場合が少なくないことが判明し，oxaliplatinのdose intensityを高める検討がなされた．2004年ASCOで発表されたOPTIMOX1(FOLFOX4 vs FOLFOX7×6+5FU/LV×12+FOLFOX7×6)の結果は両者とも奏効率：約58%，全生存期間：約20ヵ月で同等であったが，神経毒性は後者で有意に減少した[15]．現在もoxaliplatinの神経毒性を回避する目的でいくつかの臨床試験が行われている．

4．経口抗癌剤の臨床評価とその位置づけ

経口抗癌剤は主に本邦において開発され，汎用されてきた歴史がある．とくに術後補助療法ではその利便性から長期にわたり使用されてきたが十分な臨床的意義は確認されていなかった．1990年代に入り，転移性大腸癌を対象として，標準治療と考えられる5FU+LV療法を対照群として，経口抗癌剤を試験群として各薬剤複数の第III相比較試験が実施され，UFT/LVおよびcapecitabineなどが検討された[23)-27]．その結果，capecitabineのみで非劣性が検証され，アメリカにおいて大腸癌の一次治療薬として経口抗癌剤が承認されることになった．UFT/LVはUFTの配合比につき指摘され無増悪生存期間で非劣性は検証されたが，アメリカでは承認されなかった．しかし，欧州，日本では非劣性の検証がされたと判断され大腸癌に対して承認されている．

capecitabineは現在5FU+LVを含む各種併用療法において，置換可能かどうかを検討する比較試験でその併用療法での意義が検討されている．たとえば，FOLFOX療法のinfusional 5FU+LVの部分を経口抗癌剤であるcapecitabineへ置換したXELOX(capecitabine+oxaliplatin)療法[28]は第II相試験において奏効率：55%，無増悪生存期間：7.7ヵ月，生存期間中央値：19.5ヵ月とFOLFOX療法と同程度の治療成績を認めた．

この結果よりさらに，XELOX±bevacizumabおよびFOLFOX±bevacizumabの比較試験が実施された(TREE1，2試験：次項参照)．また国内でもS1とoxaliplatinとの併用療法の検討がなされているところである．これらの結果，経口抗癌剤が静注療法に置き換えることが可能となれば，利便性，医療経済性などの患者負担や臨床現場での負担が大幅に軽減することが可能となりその意義は大きい．

5．分子標的治療薬の出現

2003年のASCOにおいて，大腸癌領域においても分子標的治療薬の臨床応用がはじめて報告された．まず，bevacizumab(Avastin)の第III相試験成績[29]の報告である．本剤は，血管内皮細胞増殖因子VEGF(Vascular endotherial growth factor)に対するヒト化単クローン抗体である．IFL療法を対照群としてIFL+bevacizumab併用群を試験群として初回化学療法例を対象に比較検討がなされた．結果は，奏効率(35 vs 45%)，無増悪生存期間(6.2 vs 10.6ヵ月)，全生存期間(15.6 vs 20.3ヵ月)，のいずれにおいても併用群が有意に優れるというものであった(表4)．有害事象では出血，血小板減少，蛋白尿，高血圧などが認められ，併用群において消化管穿孔が低頻度であるが認められている．本剤は，血管新生阻害剤として初めて生存期間を延長するという事実を示し，2004年2月にはアメリカにおいて承認されている．続いて現在の標準治療の一つであるFOLFOX療法とbevacizumabの併用療法の有効性が二次治療症例を対象としたランダム化第III相試験(E3200試験)[30]で示された(生存期間中央値bevacizumab無 vs 有=10.8 vs 12.9ヵ月)(表5)．この結果を受け，現在海外においてはFOLFOX療法+bevacizumab併用療法が初回治療に対する標準治療と認識されている．さらに本レジメンの初回治療の有用性を検討した比較試験の結果(TREE1，2試験)[31)32]は2006年のASCOでその最終解析が公表され，oxaliplatinと3つの異なるフッ化ピリミジンの併用療法(mFOLFOX6，bFOL＝bolusSFU+oxaliplazin，CapeOX＝XELOX)にbevacizumabを加えることにより，毒性は忍容可能な範囲にとどまりつつ，奏効率の改善と無増悪期間, 全生存期間の延長が得られた．3群併せての生存期間中央値はbevacizumab無 vs 有=18.2 vs 24.4ヵ月とbevacizumabの併用でついに2年を超えた(表6)．

表4 IFL+Bevacizumab vs IFL 第III相試験の成績(文献29より)

	IFL+Bevacizumab	IFL
症例数	402	411
奏効率%	44.8	34.8
PFS(月)	10.6	6.2
MST(月)	20.3	15.6

PFS：無増悪生存期間 MST：生存期間中央値

また，EGFR(Epidermal growth factor receptor)に対するマウス－ヒトキメラ単クローン抗体であるcetuximab(Erbitux)も同年のASCOにおいてそのCPT-11抵抗性大腸癌に対する比較試験成績(BOND試験)[33]が報告された(表7)．EGFR陽性でCPT-11治療抵抗性の症例に対してcetuximab単独とcetuximab+CPT-11併用群を比較する試験であり，奏効率(11% vs 23%)や無増悪期間(1.5 vs 4.1ヵ月)での優位性は検証されたが，全生存期間では有意でなかった．主な有害事象はキメラ抗体であるためinfusion reactionが認められること，にきび様の皮疹，爪の変形，肺臓炎などが報告されている．本剤もヨーロッパに続き，2004年1月にアメリカにて承認された．現在，一時治療として，CRYSTAL試験(FOLFIRI±cetuximab)が，二次治療としてFOLFOX抵抗

表5 E3200試験の成績(文献30より)

	FOLFOX+BV	FOLFOX4	BV
症例数	271	271	230
奏効率%	21.8	9.2	3.0
TTP(月)	7.2	4.8	2.7
MST(月)	12.9	10.8	10.2

BV：bevacizumab　TTP：無増悪期間　MST：生存期間中央値

表6 TREE 1 および TREE2 試験の成績(文献31, 32より)

	TREE1			TREE2		
	mFOLFOX6	bFOL	CapeOx	FOLFOX+BV	bFOL+BV	CapeOx+BV
症例数	49	50	48	71	70	72
奏効率%	43	22	35	52	34	46
TTP/TTF(月)	8.7/6.6	6.9/4.9	5.9/4.4	9.9/5.8	8.5/5.3	10.3/5.5
MST(月)	19.2	17.9	17.2	28.0	20.7	27.0
MST(3群全体：月)	18.2			24.4		

BV：bevacizumab　TTP：無増悪期間　MST：生存期間中央値

表7 BOND試験の成績(文献33より)

	Cetuximab 単独群	CPT-11+Cetuximab 併用群	P-value
症例数	111	218	
奏効率%	10.8	22.9	0.0074
TTP(月)	1.5	4.1	<0.001
MST(月)	6.9	8.6	0.48

TTP：無増悪期間　MST：生存期間中央値

例に対するEPIC試験(CPT-11±cetuximab)が，また5FU，CPT-11およびoxaliplatinすべてに不応もしくは不耐容な症例に対してNCIC－CO.17試験(Best Supportive care vs cetuximab)が進行中であり，cetuximabの大腸癌におけるsurvival benefitが検証されるか，結果の解析が待たれる．さらに，完全ヒト型抗EGFR抗体であるABX-EGF(panitumumab)は，キメラ抗体であるcetuximabに比べ，infusion reactionなどの有害事象の頻度が少ないと報告されている．CPT-11およびoxaliplatinに不応となり有効な治療法がない大腸癌患者を対象にpanitumumab単剤とBSCとの比較試験が行われ，無再発生存期間においてpanitumumabが優れていた．現在，同剤とFOLFOXやFOLFIRI，bavacizmabなどとの併用療法の検討も行われている．その他にも，抗VEGF抗体としてPTK/ZK，EGFR関連チロシンキナーゼ受容体阻害剤としてgefitinib，erlotinib，lapatinibなどが臨床試験において有効性を検証されつつある．

これら新規薬剤は5FU+LV，CPT-11，oxaliplatinに続く，第4の薬剤として大きな期待が持たれているが，現在その薬剤費の高価なことがアメリカにおいては大きな問題となっている．治療開始2ヵ月間の薬剤費がbevacizumab併用で2万ドル，cetuximab併用で3万ドルという事実[34]は，個々の症例のみならず，社会全体としてこのような不治の癌患者に対する高額医療をどのよう

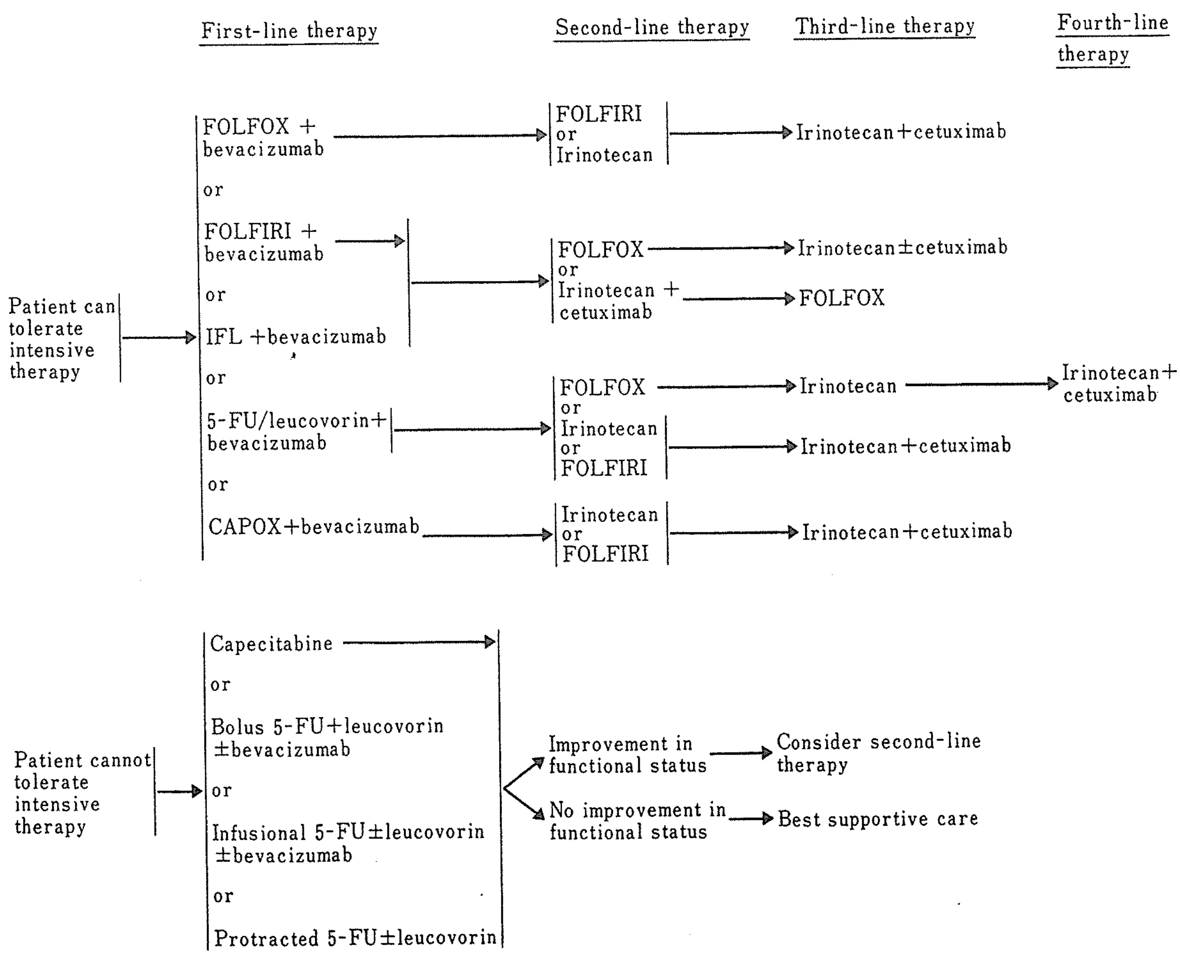
に受け入れるかのコンセンサスが必要である．

III．本邦における大腸癌化学療法の変遷と現状

本邦においては，前述したように従来経口フッ化ピリミジン製剤が主流であった．1995年にはCPT-11が承認されたが標準化使用には至らず，その後1999年にわが国での後期第II相試験の結果をもとに5-FU＋LV療法がRPMIのレジメンとして承認され，最近まで頻用されてきた．

21世紀になり現在，欧米にはかなり遅れているものの，国際的標準治療が急速に広がってきている．2003年にはUFT/LV[35]，S-1[36,37]が使用可能となった．UFT/LVは海外第III相試験成績と，日米の架橋試験成績により承認されたが，1日3回内服とLV錠の高薬価が問題である．胃癌での高い奏効率を示したS-1は大腸癌でも37%の奏効率が報告され，期待されているが，5FU+LVとの比較試験成績がなく，併用療法あるいは単独療法での比較が必須である．その後，IFLが臨床応用されるようになったが，前述の通りFOLFOX4療法に劣ることが報告され，また有害事象も強く出現しやすく早期死亡例も出現したため現在は使用が減少しつつある．2005年2月，持続点滴による5-FU+LV療法が，2005年3月にoxaliplatinが承認され，FOLFOXレジメンが本邦でも使用可能となり急速に普及した．また，FOLFIRI療法も用量の規制はあるものの使用可能となり，第II相試験が進行中である．さらにcapecitabineの海外用量での検討が終了している．bevacizumab，cetuximab，panitumumabなどの分子標的薬剤も第II相試験が行

表8 Chemotherapy for advanced or metastatic disease(文献40より)



われている段階で，承認は早くて2007年となる見込みである．肝動注療法は，全身化学療法と比して腫瘍縮小効果は優れているものの，肝外病変の出現などが問題であり，現在肝動注＋CPT-11全身投与の第II相試験が進行中であるが，survival benefitが検証されるか，その評価はいまだ定まっていない．

以上より，本邦では現時点ではFOLFOX，FOLFIRIまたはIFLが，進行大腸癌に対する第一選択の治療とされる．高齢者やPS不良例では5FU/LVやUFT/LV，S-1などが選択肢となりうる．これらは2005年7月に大腸癌研究会から発表された「大腸癌治療ガイドライン[38]」にも記されている．一方，海外ではNCI-PDQ[39]や全米癌総合ネットワーク(National Comprehensive Cancer Network：NCCN)[40](表8)などにおいてweb上で治療法選択のガイドラインが公表されており，腫瘍専門医がこの情報をもとに治療法を選択するという流れが起こっている．本邦においても，同様のガイドラインをwebなどを利用して公表，タイムリーに更新し，地域格差および病院間格差の解消に努めるべきと考える．

ま と め

大腸癌に対する抗癌剤治療は，1990年代後半から10年足らずの間に大きな変貌を遂げた．科学的に計画された臨床試験の積み重ねにより，最短時間で新規治療法の評価と一般化を進め，切除不能転移性大腸癌の生存期間は無治療の8ヵ月から今や2年を超える時代となった(図1)．CPT-11，oxaliplatin，capecitabineなどは，本邦で開発された薬剤であるにもかかわらず，臨床応用については現在，欧米にかなり遅れをとっていることは否めない．今後，分子標的薬剤をはじめとした新規抗癌剤が可及的早期に承認が得られるようなシステムの構築や，安全性，有効性を検証する多施設共同の臨床試験が迅速に実施できるネットワークの確立，さらには欧米との格差を少しでも縮めていこうとする自覚と患者のQOLや医療経済的概念も念頭においた適切な治療法の選択ができる臨床能力が個々の腫瘍専門医に求められている．

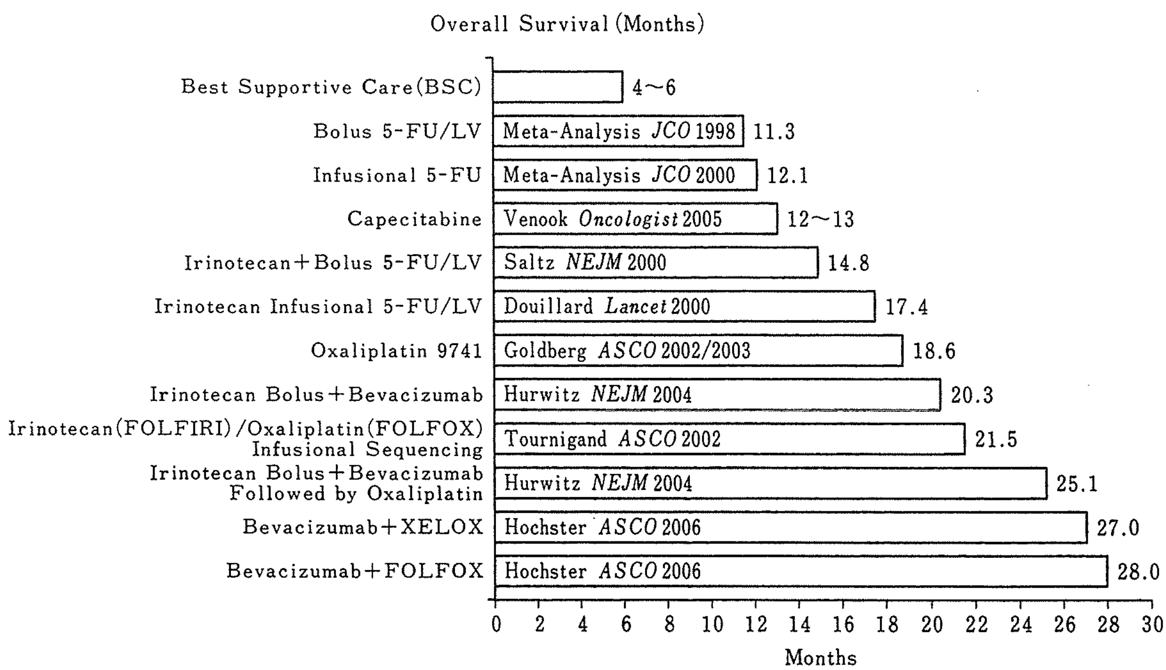


図1　大腸癌治療の流れと生存期間の推移(文献19，32，41より)

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Short Time to Recurrence After Hepatic Resection Correlates with Poor Prognosis in Colorectal Hepatic Metastasis

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Background: Early recurrence is a major problem after hepatic resection of colorectal hepatic metastasis (CHM). Our aim was to investigate the relationship between time to recurrence after CHM resection and overall survival.
Methods: A retrospective analysis was performed for 101 consecutive patients who underwent hepatic resection for CHM and have been followed more than 5 years.
Results: Among 101 patients, 82 (81%) had a recurrence. Overall survival of patients with recurrence within 6 months after CHM resection was significantly worse than that of patients with recurrence after more than 6 months ($P < 0.01$). Overall survival was poorer when time to recurrence was shorter. One of the reasons for poor prognosis of patients with recurrence within 6 months was that only a few patients could undergo a second resection for recurrence after CHM resection. Histological type, including poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor, bilobar metastases, microscopic positive surgical margin and carcinoembryonic antigen (CEA) above 15 ng/ml had predictive value for decreased recurrence-free survival after CHM resection.
Conclusion: Short time to recurrence after CHM resection correlates with a poor prognosis. Histological type of poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor might be a predictor for early recurrence after CHM resection.

Key words: colorectal cancer – hepatic metastasis – resection – recurrence

INTRODUCTION

Hepatic resection is currently the only potentially curative treatment for colorectal hepatic metastasis (CHM) (1–6). However, frequent recurrence is a major problem after surgery, with 80–85% of patients experiencing a recurrence (2,3,6). Thus, reduction of recurrence is necessary to improve prognosis after CHM resection.

A correlation between a short time to recurrence after resection of the primary tumor and poor prognosis after resection of recurrence has been demonstrated in colorectal cancer (2,5), breast cancer (7), hepatocellular carcinoma (8) and renal cell carcinoma (9). In CHM, however, the correlation between time to recurrence after resection for CHM and prognosis is still obscure. The relation between time to recurrence after resection and prognosis is complicated in CHM because many recurrences after CHM resection can be resected, and resection sometimes contributes to long-term survival (10–12).

This study was conducted to determine the correlation between time to recurrence after CHM resection and prognosis by scrutinizing recurrence after CHM resection, which may suggest the best timing for adjuvant chemotherapy and elucidate whether time to recurrence can be a surrogate endpoint for adjuvant study in resectable CHM. We also compared clinicopathological factors and time to recurrence to find out preoperative predictive factors for early recurrence.

PATIENTS AND METHODS

Patient Population

A total of 101 patients who had undergone hepatic resection for CHM at the National Cancer Center Hospital East between September 1992 and January 2000 and have been followed precisely for more than 5 years were examined retrospectively. The patients consisted of 56 (55%) men and 45 (45%) women, ranging in age from 23 to 78 years (mean, 60 years). None of the patients had received adjuvant chemotherapy after primary colorectal resection.

The criteria for hepatectomy were as follows: metastatic lesions were confined to the liver and all lesions could be

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resected using oncologic principles while preserving liver function. Extended lobectomy plus partial resections were considered as the upper limit of hepatectomy that could be performed safely, and trisegmentectomy was applied only when the volume of the residual liver was deemed to be abundant. Neither the number of metastatic tumors nor tumor size, in themselves, excluded patients from hepatectomy.

No patient received adjuvant therapy after CHM resection.

Surgical Procedure

After laparotomy, a careful search was performed for local recurrences, extrahepatic metastases and peritoneal dissemination in the abdominal cavity. Any suspicious lesions were examined by biopsy. If the regional lymph nodes (hepatoduodenal or peripancreatic lymph nodes) were positive, dissection of the regional lymph nodes was performed. Intraoperative bimanual liver palpation and ultrasonography were performed to confirm tumor location and size of the lesions in all patients; all resections were ultrasound-guided procedures. Hepatic resection was performed with tumor-free resection margins using the forceps fracture method under inflow occlusion (Pringle's maneuver).

Clinical Follow-up

After hepatic resection, patients were closely followed up with diagnostic imaging (chest X-ray and abdominal CT every 3 months, measurement of serum carcinoembryonic antigen (CEA) levels every month and annual colonoscopy to detect tumor recurrence) up to 5years. After 5 years patients were followed up every 6 months or annually.

Morphologic Investigations

The resected colorectal specimens and hepatic specimens were fixed in 10% phosphate-buffered formalin and cut at intervals of 5 mm and 10 mm, respectively, and then embedded in paraffin. Serial sections of 3 μm thickness were stained with hematoxylin and eosin for morphologic examination. Histological diagnosis was performed according to the World Health Organization intestinal tumor classification (13).

Statistical Analysis

The chi-square test and student *t*-test were used to compare data (Dukes' stage, primary location, positive regional lymph node, size of tumor, number of tumors, synchronous/metachronous, tumor distribution and ratio of recurrence) between subgroups based on time to recurrence. Mann–Whitney's *U*-test was used to compare preoperative serum CEA level between subgroups. Analyses of survival were performed using the Kaplan–Meier method (14), and differences between the curves were tested using the log-rank test. The log-rank test was also used to examine the significance of associations between survival curves and CEA cutoff values of 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 and 200 ng/ml.

Factors related to survival were analyzed with the Cox proportional hazards regression model (15). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Surgical Resections

Partial resection was performed on 47 patients, subsegmentectomy on 9, segmentectomy on 25, lobectomy on 11, extended lobectomy on 6 and trisegmentectomy on 3 according to Couinaud's anatomical classification (16). A microscopic positive surgical margin was observed in 14 patients. There was no perioperative mortality. Twenty-one complications were observed: 7 cases of biliary leak; 6 cases of intra-abdominal abscess; 4 cases of wound infection; and 1 case each of liver failure, ileus, lung abscess and urinary tract infection.

Survival After CHM Resection

The overall 5-year Kaplan–Meier survival rate after hepatic resection for CHM was 42%, with a median survival of

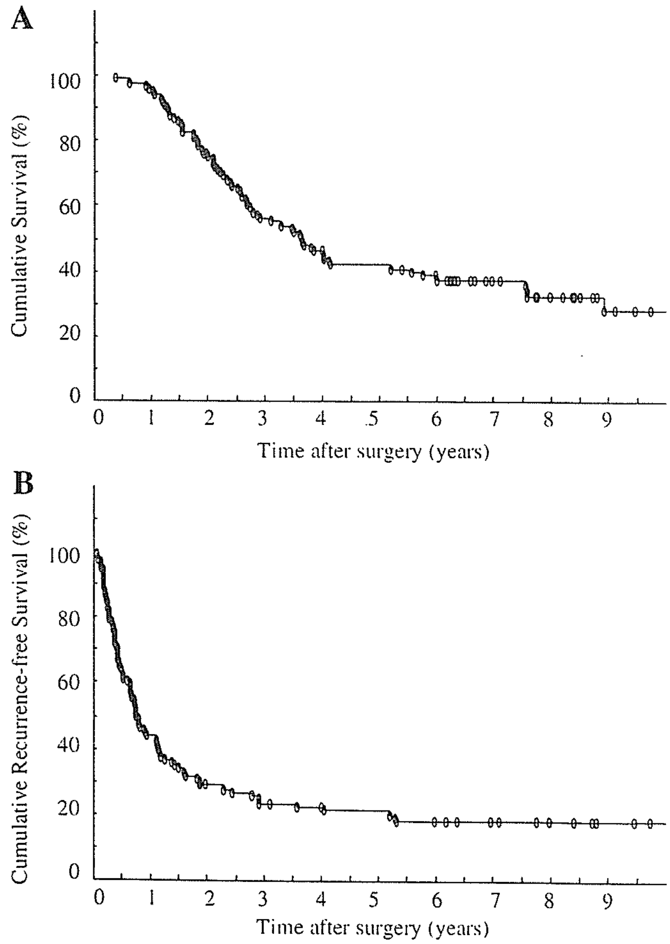

Figure 1. Cumulative survival (A) and recurrence-free survival curves (B) for 101 patients with resected colorectal hepatic metastasis.

34 months (Fig. 1A). Recurrence-free 1-, 3- and 5-year survival rates were 43, 23 and 21%, with a median recurrence-free survival of 9 months (Fig. 1B). The median follow-up duration of survivors was 87 months.

Recurrences After CHM Resection (Fig.2)

Among the 101 patients who underwent CHM resection, 82 (81%) developed recurrences. Locations of recurrences were as follows: liver in 36 patients, lung in 17, both liver and lung in 9, lymph node in 6, peritoneum and local recurrence in 4 each, brain and adrenal gland in 2 each, and ovary and bone in 1 each. Thirty-seven recurrences (45%) occurred within 6 months after hepatic resection and 72 recurrences (88%) occurred within 2 years. The ratio of hepatic recurrences to total recurrences was significantly higher in 1st–12th month than that after 12th month from CHM resection ($P = 0.01$). The ratio of pulmonary recurrence and that of recurrence in organs other than the liver and lung were significantly higher after 24th month ($P < 0.05$) and in 13th–24th month ($P < 0.05$) from CHM resection, respectively, than those in the other period. Of the 82 patients with recurrence after hepatic resection 36 received re-resection. Re-resection could be performed in only 10 of 24 patients (42%) whose recurrence occurred in the liver or lung within 6 months after hepatic resection, whereas re-resection could be performed in 22 of 29 patients (76%) whose recurrence occurred in the liver or lung more than 6 months later ($P = 0.01$). Of the remaining 46 patients, 33 received systemic chemotherapy, 7 received hepatic arterial infusion, 2 received radiation therapy and 4 received best supportive care.

Clinicopathological Features According to Time to Recurrence

Table 1 summarizes the primary and metastatic tumor characteristics. Patients were classified into three subgroups according to time to recurrence after hepatic resection as follows: no recurrence, recurrence within 6 months and recurrence after more than 6 months. There were no significant differences in primary tumor characteristics between the three subgroups. All patients in the no recurrence group had a primary tumor that was classified as a well- or moderately differentiated carcinoma.

In terms of characteristics of the metastatic tumor, the number of tumors was significantly less ($P < 0.01$) and unilobar distribution was seen significantly more frequently ($P < 0.01$) in the no recurrence group compared with the other subgroups.

Survival According to Time to Recurrence

Kaplan–Meier curves for overall survival after CHM resection according to time to recurrence in patients who developed recurrences are shown in Fig. 3A. Patients were divided into four subgroups according to time to recurrence after hepatic resection as follows: within 6 months, 7th–12th month, 13th–24th month and after 24th month. Overall survival of

Resection n=101

↓

Recurrence n=82

Time to recurrence	n	%	Location			
			Liver (resected case)	Lung	Liver + Lung	Others
–6 months	37	45.1	19 (8)	5 (2)	6 (0)	7 (1)
7–12 months	20	24.4	11 (7)	3 (2)	2 (1)	4 (1)
13–24 months	15	18.3	3 (3)	3 (2)	1 (0)	8 (1)
25– months	10	12.2	3 (3)	6 (5)		1 (0)

Figure 2. Locations of recurrence according to time to recurrence after resection of colorectal hepatic metastasis. The number of resected cases for the recurrence is shown in parentheses.

Table 1. Clinicopathological findings of 101 patients with colorectal hepatic metastases according to time to recurrence

Variable	No recurrence (19)	Recurrence within 6 months (37)	Recurrence after more than 6 months (45)	*P*-value*
Primary colorectal tumor				
TNM Classification				0.63
I	1	1	2	
II	4	11	6	
III	10	12	21	
IV	4	13	16	
Location				0.85
Rectum	4	7	17	
Colon	15	30	28	
Number of positive lymph nodes (mean ± SD)	1.3 ± 2.1	2.3 ± 3.8	1.4 ± 1.7	0.29
Histological type of adenocarcinoma				
Well- or moderately differentiated	19	33	42	
Poorly differentiated signet ring cell or mucinous	0	4	3	
Hepatic metastases				
Maximum size of tumor (mean ± SD, cm)	4.5 ± 3.1	3.6 ± 2.1	4.3 ± 3.3	0.26.
Number of tumors (mean ± SD)	1.3 ± 0.6	2.5 ± 1.6	1.9 ± 1.4	<0.01
Preoperative CEA level (mean ± SD, ng/ml)	264.0 ± 818.0	41.3 ± 53.8	220.7 ± 879.7	0.25
Synchronous/metachronous				0.94
Synchronous	7	14	18	
Metachronous	12	23	27	
Distribution of metastases				<0.01
Unilobar	18	20	29	
Bilobar	1	17	16	

SD, standard deviation; CEA, carcinoembryonic antigen.
*Difference between patients with no recurrence and those with recurrence within 6 months.

patients with recurrence within 6 months after resection was significantly worse than that of patients with recurrence in 7th–12th month ($P = 0.04$), that of patients with recurrence in 13th–24th month ($P < 0.01$) and that of patients with recurrence after 24th month ($P < 0.01$). Overall 5-year survival rate in patients who developed recurrence within 6 months after hepatic resection was only 10% with a median survival of 26 months. Overall survival was poorer when time to recurrence was shorter.

Figure 3B shows overall survival after recurrence according to time to recurrence. Overall survival after recurrence of patients with recurrence within 6 months after resection was still worse than that of patients with recurrence in 13th–24th month ($P < 0.04$) and that of patients with recurrence after 24th month ($P < 0.03$). Overall survival after recurrence of patients with recurrence in 7th–12th month after resection seemed to be better than that of patients with recurrence within 6 months, but the difference was not significant ($P = 0.14$). Survival after recurrence tended to be poorer when time to recurrence was shorter. Overall survival after recurrence of patients with recurrence within 6 months after resection was significantly worse than that of patients with recurrence in more than 6 months ($P < 0.01$).

Correlation Between Clinicopathological Factors and Recurrence-free Survival

To find prognostic factors for recurrence-free survival after CHM resection, correlations between clinicopathological factors and recurrence-free survival were analyzed (Table 2). Histological type of tumor, including poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor ($P < 0.01$) (Fig. 4), two or more hepatic tumors ($P < 0.01$), bilobar distribution ($P < 0.01$), microscopic positive surgical margin ($P = 0.03$) and CEA level before hepatic resection above 15 ng/ml ($P = 0.04$) were significantly associated with poor recurrence-free survival.

We examined the independent predictive value of the aforementioned factors in recurrence-free survival. Data were analyzed using a Cox regression model (Table 3). Histological type of poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor [$P < 0.01$;

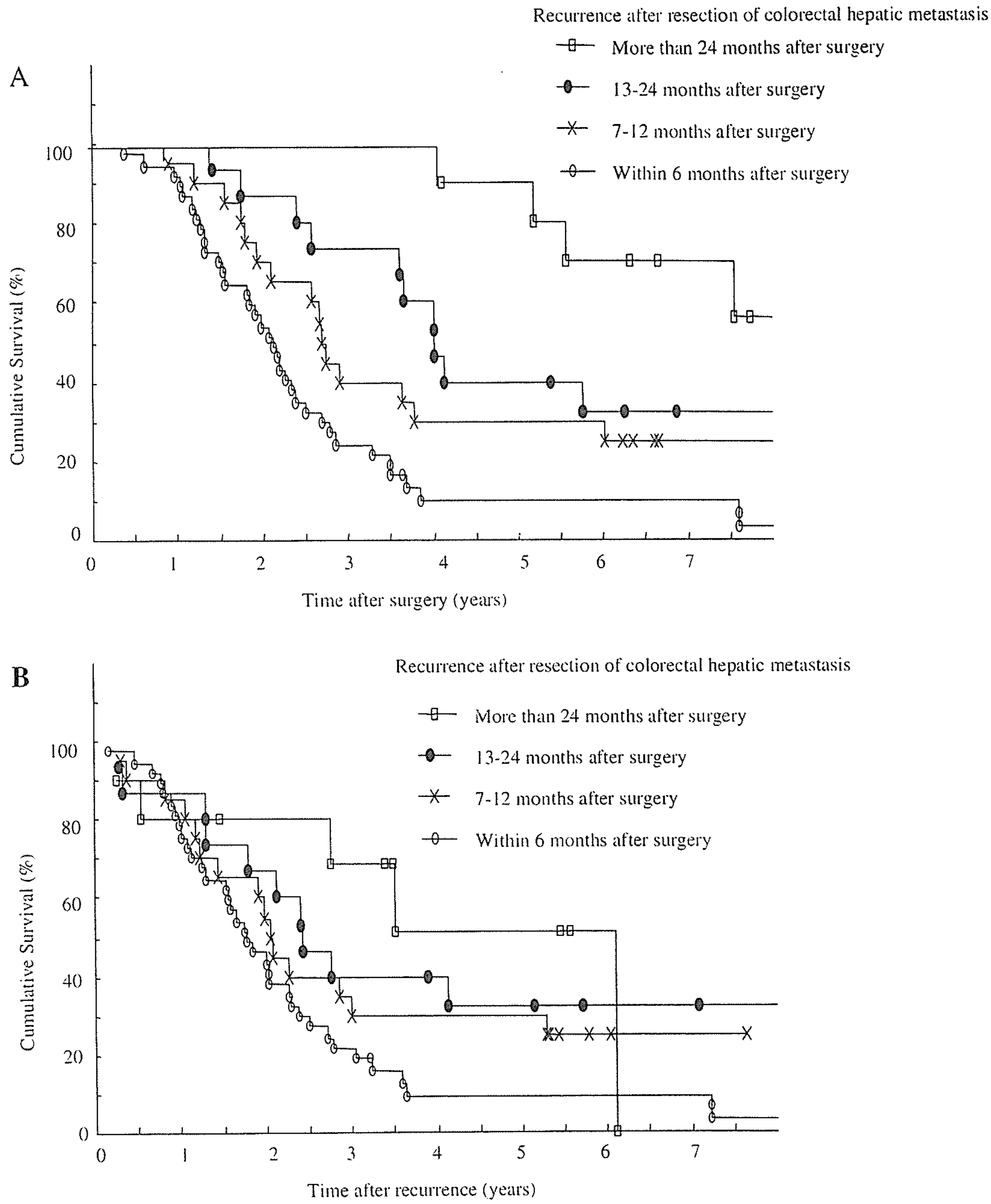

Figure 3. (A) Cumulative survival curves after resection of colorectal hepatic metastasis according to the time to recurrence. (B) Cumulative survival curves after recurrence after resection of colorectal hepatic metastasis according to the time to recurrence.

relative risk (RR) = 5.16; 95% confidence interval (CI), 2.10–12.69], bilobar metastases (P = 0.04; RR = 2.73; 95% CI, 1.03–7.27), microscopic positive surgical margin (P = 0.03; RR = 2.25; 95% CI, 1.11–4.59) and CEA level above 15 ng/ml (P = 0.02; RR = 1.96; 95% CI, 1.09–3.55) had a predictive value for decreased recurrence-free survival after CHM resection. Median disease-free survivals and 1-year recurrence rates of patients with the aforementioned factors were 4.6, 5.6, 5.0 and 8.4 months and 100, 70, 79 and 65%, respectively.

Histological type of poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor and CEA level above 15 ng/ml were also the poor prognostic factors for overall survival (data not shown).

DISCUSSION

The goal of this study was to assess the correlation between time to recurrence after CHM resection and prognosis. Results showed that prognosis of patients with recurrence within 6 months after resection was significantly worse than that of patients with recurrence after more than 6 months. Our findings indicate that short time to recurrence after CHM resection correlates with a poor prognosis.

The main reason for poor prognosis of patients with recurrence within 6 months was that only a few patients could undergo a second resection for recurrence after CHM resection. Most patients who could not undergo a second resection

Table 2. Correlation between clinicopathological factors and disease-free survival after hepatectomy for colorectal hepatic metastases

Variable	No. of patients	Median disease-free survival (months)	*P*-value
Primary colorectal lesion			
Location			
Colon	73	9.0	0.67
Rectum	28	9.5	
TNM Classification			
I, II	25	6.2	0.87
III, IV	76	9.6	
Lymph node metastasis			
Absent	35	9.0	0.79
Present	66	9.5	
Histological type of adenocarcinoma			
Well- or moderately differentiated	94	11.3	<0.01
Poorly differentiated signet ring cell or mucinous	7	5.1	
Hepatic metastases			
Number of tumors			
Solitary	58	13.6	<0.01
≥2	43	5.9	
Maximum size of the tumor (cm)			
<5	77	9.0	0.58
≥5	24	13.4	
Distribution of metastases			
Unilobar	67	13.5	<0.01
Bilobar	34	5.7	
Microscopic surgical margin			
Negative	87	10.3	0.03
Positive	14	6.4	
CEA level before treatment (ng/ml)			
<15	47	15.4	0.04
≥15	54	8.4	
Synchronous/metachronous			
Synchronous	39	9.1	0.84
Metachronous	62	9.3	
Interval between colorectal resection and hepatectomy			
<1 year	65	7.8	0.11
≥1 year	36	13.5	

CEA, carcinoembryonic antigen.

had extensive disease such as hepatic or pulmonary recurrence with much tumor burden, recurrence involving multiple organs, or distant metastases outside liver and lung that were not suitable for resection. In this series, re-resection rates of recurrence in the remnant liver and lung were relatively low (42 and 40%, respectively) when recurrences were observed within 6 months after CHM resection, whereas they were high (76 and 75%, respectively) when recurrences were observed more than 6 months after resection.

Tumor doubling time is correlated with prognosis in various cancers (17–20). In CHM, it has been reported that short tumor doubling time is a poor prognostic factor for both overall and disease-free survival (21). Short time to recurrence represents short tumor doubling time. Those results are in accord with those of the present study.

Our results suggest that recurrence-free survival can be a surrogate endpoint for adjuvant trial in resectable CHM. Moreover, recurrence within 6 months should be a major target for additional chemotherapy because of a great number and the poor prognosis of these patients. Theoretically, if we can determine which patients will have a recurrence with short recurrence-free survival, we could identify which ones would possibly benefit from neoadjuvant chemotherapy. Adam *et al.* (22) showed efficacy of neoadjuvant chemotherapy for CHM patients with four or more tumors regardless of initially resectable or not, as long as objective tumor response or stabilization was achieved by chemotherapy, and demonstrated the possibility of neoadjuvant chemotherapy for resectable CHM. However, neoadjuvant chemotherapy sometimes causes chemotherapy-associated steatohepatitis which may increase operative morbidity (23,24); then, neoadjuvant chemotherapy should be recommended for high-risk patients for recurrence.

In the present study, histological type of poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor, bilobar metastases, microscopic positive surgical margin and CEA above 15 ng/ml were the independent prognostic factors for poor recurrence-free survival. Especially, histological type of poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor exhibited the strongest power for predicting early recurrence because all patients with the factor had recurred within 10 months. Then, histological type of poorly differentiated signet ring cell or mucinous adenocarcinoma in the primary tumor, which was not considered in other large studies (2,5), should be considered as one of the preoperative predictors of early recurrence after CHM resection. Patients with the factor are recommended to receive neoadjuvant chemotherapy. Bilobar metastases and CEA above 15 ng/ml were also prognostic factors for recurrence; however, long-term recurrence-free survival was achieved in some patients with the factors. Neoadjuvant chemotherapy for patients with either of the factors is controversial. In addition, considering the correlation between positive surgical margin and early recurrence, hepatic surgeons should pay much attention to keep negative surgical margin during hepatic dissection in order to prevent early recurrence.

In a retrospective analysis of consecutive 1001 CHM patients by Fong *et al.* (5), poor prognostic factors for recurrence after CHM resection were positive surgical margin, extrahepatic disease, node-positive primary, less than

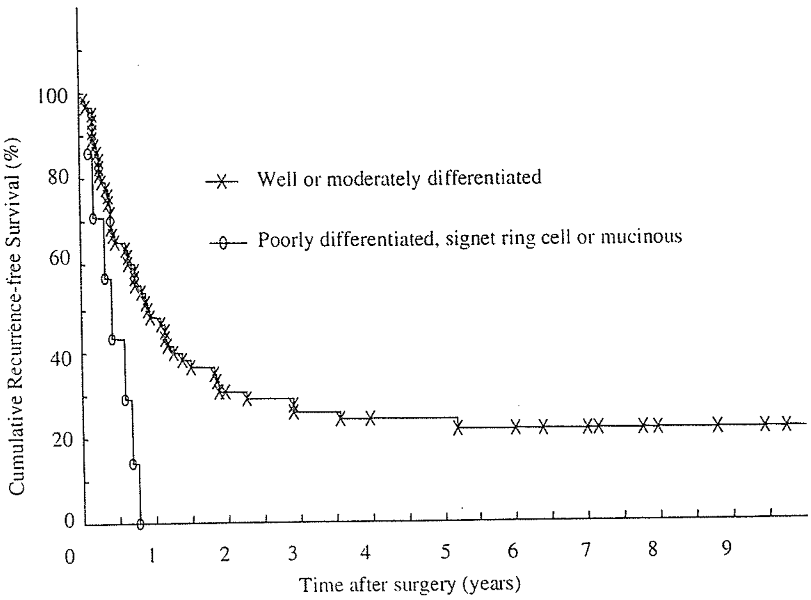

Figure 4. Recurrence-free survival curves after resection of colorectal hepatic metastasis according to the histological type of primary tumor.

Table 3. Multivariate analyses of factors affecting disease-free survival after hepatectomy for colorectal hepatic metastases

Variable	Relative risk (95% CI)	*P*-value
Primary colorectal lesion		
Histological type of adenocarcinoma		
Well- or moderately differentiated	–	<0.01
Poorly differentiated signet ring cell or mucinous	5.16 (2.10–12.69)	
Hepatic metastases		
Number of tumors		
Solitary	–	0.60
⩾2	1.29 (0.50–3.38)	
Distribution of metastases		
Unilobar	–	0.04
Bilobar	2.73 (1.03–7.27)	
Microscopic surgical margin		
Negative	–	0.03
Positive	2.25 (1.11–4.59)	
CEA level before treatment (ng/ml)		
<15	–	0.02
⩾15	1.96 (1.09–3.55)	

CI, confidence interval; –, reference.

12 months of disease-free interval from the primary resection, 2 or more tumors, tumor size >5 cm and CEA >200 ng/ml. The aforementioned prognostic factors for recurrence were also predictors of poor overall survival, and the fact was consistent with the concept of our results that short time to recurrence correlated with poor survival. Fong *et al.* proposed a scoring system using five poor prognostic factors and insisted that the scoring system was useful in choosing adjuvant therapy.

The difference between our results and those of Fong's might be partly due to patients' background and the number of patients examined. In the present study, patients with extrahepatic disease were excluded because CHM with extrahepatic disease was totally different from pure CHM considering pathways of metastases. Moreover, none of the patients had received adjuvant chemotherapy after primary colorectal resection or CHM resection. However, the possibility that not all of Fong's predictors could be validated well because of relatively small population of our study cannot be ruled out.

In the present study, patients were followed and examined precisely at least for 5 years in order to elucidate complete profile of recurrence, and then median follow-up of survivors was 87 months. This study has clarified frequencies of the recurrences after CHM resection in liver, lung and other organs respectively according to time to recurrence and also clarified the resection-rates for those recurrences. On the result of the present study, the organ where recurrence had occurred most frequently and the resection-rate for the recurrences differed according to time to recurrence after CHM resection. Frequency of hepatic recurrence decreased rapidly after 2 years of CHM resection; however, that of pulmonary recurrence was not low even more than 2 years after CHM resection. A periodical checkup by chest XP or chest CT adding to abdominal examination is recommended for 5 years at least.

In conclusion, short time to recurrence after CHM resection correlates with a poor prognosis. This result provides grounds for proposal that an effective neoadjuvant chemotherapy and a system using the clinicopathological factors and pharmacogenetics which identify best candidates for the neoadjuvant chemotherapy are needed in order to reduce early recurrence. Histological type of primary tumor might be a strong predictor for early recurrence after CHM resection.

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Importance of intra-individual variation in tumour volume of hepatic colorectal metastases

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Abstract

Aims: The efficacy of surgical resection for multiple colorectal hepatic metastases (MCHM) has been controversial. We examined the survival of patients who received surgery for MCHM and examined the factors associated with survival.
Methods: A retrospective analysis was performed of 50 consecutive patients who received hepatic resections for MCHM, defined as four or more metastatic lesions of colorectal cancer.
Results: Overall survival after hepatic resection for MCHM was 48% at 3 years and 43% at 5 years (median survival, 22.3 months). Multivariate analyses revealed that a coefficient of variation (CV) in volume of hepatic metastases in each individual patient above 1.8 ($P = 0.01$, HR = 4.08, 95% CI = 1.33–12.5) was the only poor prognostic factor after resection of MCHM.
Conclusions: A CV in volume of hepatic metastases in each individual patient above 1.8 predicts poor survival after hepatectomy of MCHM. Thus, the CV in volume of hepatic metastases in each individual patient might be useful in planning the therapeutic strategy for patients with MCHM.

Keywords: Colorectal cancer; Hepatic metastases; Resection; Tumour volume; Coefficient of variation

Introduction

Hepatic resection is currently the only potentially curative treatment and the first-line therapy for colorectal hepatic metastasis.[1–5] The efficacy of hepatic resection has been reported for some cases of multiple colorectal hepatic metastases (MCHM); Bolton et al. reported that the survival of patients who underwent resection of more than four and/or bilobar hepatic metastases was equivalent to that of patients who underwent resection of fewer than four and unilobar hepatic metastases.[6] Nevertheless, hepatic resection for MCHM has been controversial because several reports demonstrated that having fewer lesions is a favorable prognostic factor after hepatic resection of colorectal hepatic metastases.[5,7–13]

Therefore, this study was conducted to evaluate the efficacy of resection for MCHM and elucidate any prognostic factors that could identify the patients who would benefit from surgical resection for MCHM. We focused on the histology of the tumour, tumour volume ratio (tumour volume/whole liver volume), and dispersion (coefficient of variation) of volume of hepatic metastases in each patient. We defined MCHM as four or more metastatic lesions of colorectal cancer of the liver, because four metastases corresponds to the limit of surgical resectability most widely used during the past decade.[6,14]

Patients and methods

Definition of MCHM

MCHM was defined as four or more metastatic lesions of colorectal cancer in the liver. Patients who showed any

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metastatic lesion outside the liver were excluded from the MCHM group. The diagnosis of MCHM was confirmed by diagnostic imaging before treatment.

Patient population

The records of 370 patients who had undergone hepatic resection for colorectal hepatic metastasis at the National Cancer Center Hospital East between September 1992 and August 2005 were examined retrospectively. Fifty of these patients met the criteria for MCHM. The patients consisted of 34 men and 16 women, ranging in age from 44 to 85 years, with a mean age of 60 years. Two of the patients had received oral uracil/tegafur and five had received 5-fluorouracil (5-FU)-leucovorin (LV) as adjuvant chemotherapy after primary colorectal resection. Few use of adjuvant chemotherapy after primary colorectal resections in our series ascribed to the fact that adjuvant chemotherapy has been rarely used after primary colorectal resections in our institution until 2002 although all patients with stage III colorectal cancer has received either 5-FU-LV or oral uracil/tegafur-LV since 2002.

The criteria for hepatectomy were as follows: metastatic lesions were confined to the liver and all lesions could be resected using oncologic principles (tumour-free margin and no residual disease) while preserving liver function. Basically, extended lobectomy plus partial resections was considered as the upper limit of hepatectomy that could be performed safely, and trisegmentectomy was applied only when the volume of the residual liver was deemed to be thoroughly abundant. Neither the number of metastatic tumours nor tumour size alone excluded patients from hepatectomy.

Irinotecan/5-FU/LV has been administered after hepatic resection of colorectal metastasis since 2003 when patients want to receive adjuvant chemotherapy; 9 patients in this study received the adjuvant therapy.

Operative procedure

After laparotomy, a careful search was performed for local recurrence, extrahepatic metastases, and peritoneal dissemination in the abdominal cavity. Any suspicious lesions were examined by biopsy. If metastasis in the regional lymph nodes (hepatoduodenal or peripancreatic lymph nodes) was suspected by preoperative imaging diagnosis or intraoperative findings, dissection of the regional lymph nodes was performed. Intraoperative bimanual liver palpation and ultrasonography were performed to confirm tumour location and size of the lesions in all patients, and all of the resections were ultrasound-guided procedures. Hepatic resection was performed with tumour-free resection margins by the forceps fracture method under inflow occlusion (Pringle's maneuver). Blood loss and operative time were recorded.

Clinical follow-up

After hepatic resection, patients were closely followed up with diagnostic imaging [chest X-ray and abdominal computed tomography (CT)] every 3 months, measurement of serum carcinoembryonic antigen (CEA) levels every month, and an annual colonoscopy to detect any tumour recurrence. The median follow-up duration of survivors was 27 months.

Measurement of tumour volume

Tumour volumes were obtained from helical CT scans of the abdomen, which were performed in all patients before initial treatment using 5-mm collimation after administration of 120 cc of non-ionic intravenous contrast injected at 2 cc per second with a 60-s delay. Images were reconstructed at 5-mm intervals using a standard soft-tissue algorithm.

Metastatic lesions and the whole liver were outlined manually on each axial slice using a computer mouse. The volume of metastatic lesions and that of whole liver were calculated automatically by multiplying the sum of the areas from each slice by the reconstruction interval. Then, tumour volume ratio was calculated (volume of tumour/volume of whole liver × 100%). All measurements were made by one radiologist.

For statistical analysis of inter-tumour variability in volume, in other words, dissimilarity in volume of metastases in each single patient, the coefficient of variation (CV; SD of the mean divided by the mean) was calculated for each case.

Histological parameters

The resected colorectal specimens and hepatic specimens were fixed in 10% phosphate-buffered formalin and cut at intervals of 5 mm and 10 mm, respectively, and then embedded in paraffin. Serial sections of 3-μm thickness were stained with hematoxylin and eosin (H&E) for morphological examination. Each case was histologically classified according to the histological type, tumour size, location, number of metastases, presence of serosal invasion, nodal status, and margin status. Histological diagnosis was performed according to the World Health Organization intestinal tumour classification.[15]

Statistical analysis

Analyses of survival were performed using the Kaplan–Meier method[16] and differences between the curves were tested using the log-rank test. The log rank test was also used to examine the significance of associations between survival curves and the following: CEA cutoff values 10 ng/ml, 20 ng/ml, 30 ng/ml, 50 ng/ml, 70 ng/ml, 100 ng/ml, and 200 ng/ml; tumour volume ratio cutoff values

1%, 3%, 5%, 8%, 10%, and 20%; and CV in tumour volume cutoff values 1.2, 1.4, 1.6, 1.8, and 2.0. Factors related to survival were analyzed with the Cox proportional hazards regression model.[17] A P value of less than 0.05 was considered to denote significance.

Results

Clinicopathological features of patients with MCHM

Fifty patients underwent resection of MCHM at the National Cancer Center Hospital East. Table 1 summarizes the primary and metastatic tumour characteristics. Four liver tumours were found in 20 patients, 5 tumours in 12, 6 tumours in 8, 7 and 8 tumours in 3 each, 9 tumours in 2, and 10 and 11 tumours in 1 each. Neither hepatoduodenal nor peripancreatic lymph node metastasis was found in any patient.

Surgical resections

Multiple partial resections were performed on 24 patients, segmentectomy on 12, lobectomy on 10, extended lobectomy on 2, and central bi-segmentectomy on 2 according to Couinaud's anatomical classification.[18] Forty-two of the 50 patients underwent multi-site resections. Microscopically positive surgical margins were observed in 11 patients. There was no perioperative mortality. Eleven complications were observed: five cases of biliary leak, two cases of intra-abdominal abscess, two cases of anastomotic leak in patients with synchronous metastases, one case of postoperative bleeding, and one case of liver failure.

Table 1
Clinicopathological findings of 50 patients with multiple colorectal hepatic metastases

	No. of patients
Primary colorectal tumour	
Stage (TNM classification)	
I	2
II	8
III	14
IV	26
Location	
Rectum	19
Colon	31
Maximum size of tumour (mean ± SD, cm)	4.9 ± 1.9
Histological type of adenocarcinoma	
Well or moderately differentiated	46
Poorly differentiated and others	4
Hepatic metastases	
Maximum size of tumour (mean ± SD, cm)	3.7 ± 2.3
Number of tumours (mean ± SD)	5.4 ± 1.8
Preoperative CEA level (mean ± SD, ng/ml)	65.4 ± 142.2
Synchronous/Metachronous	
Synchronous	24
Metachronous	26
Distribution of metastases	
Unilobar	12
Bilobar	38
Sum of the tumour volume (mean ± SD, cm^3)	61.2 ± 86.4
Tumour volume ratio* (mean ± SD, %)	4.8 ± 6.3
Coefficient of variation† in tumour volume (mean ± SD)	1.2 ± 0.6
Interval between resection of primary site and resection of hepatic metastases (median, mo)	7.9

SD, standard deviation; CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Recurrences after resection of MCHM

Among the 50 patients, 37 developed recurrences. Locations of recurrence were as follows: liver in 32 patients, lung in 8, lymph node in 4, local recurrence in 3, peritoneum in 2, and bone and ovary in 1 each. Ten patients underwent resection for hepatic recurrences, 2 underwent resection for pulmonary recurrences, and one underwent resection for both hepatic and pulmonary recurrences. Of the remaining 24 patients, 19 received systemic chemotherapy, 2 received hepatic arterial infusion, and 3 received optimal supportive care.

Overall survival

Kaplan–Meier curve for overall survival after resection of MCHM is shown in Fig. 1. Actuarial overall survival after resection of MCHM was 48% at 3 years and 43% at 5 years with a median survival of 22.3 months. Meanwhile, overall survival of the entire cohort of 370 patients was 58% at 3 years and 46% at 5 years with a median survival of 27.6 months.

Association between clinicopathological factors and overall survival

To find prognostic factors for survival after resection of MCHM, clinicopathological factors and overall survival

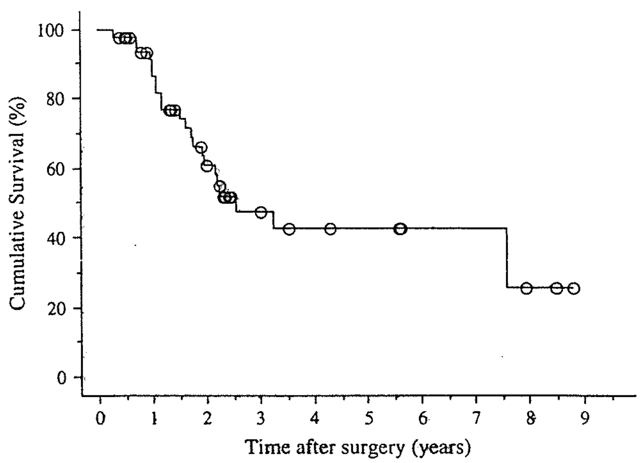

Figure 1. Cumulative survival curve for 50 patients with resected MCHM. The survival curve was generated by Kaplan–Meier analysis.

were analyzed in the 50 patients with MCHM (Table 2). Maximum tumour size above 5 cm ($P = 0.02$), CEA level before hepatectomy above 20 ng/ml ($P = 0.01$), tumour volume ratio above 8% ($P = 0.04$), and CV in tumour volume above 1.8 ($P < 0.01$) were significantly associated with poor overall survival.

We examined the independent predictive value of the aforementioned factors in overall survival. The data were analyzed using a Cox regression model (Table 3). Maximum size of the tumour was excluded from the analysis because it was strongly correlated with tumour volume. Then, only CV in tumour volume above 1.8 ($P = 0.01$; HR = 4.08; 95% CI, 1.33 to 12.5) had predictive value for decreased overall survival after resection of MCHM. Fig. 2 shows a case of MCHM with low CV (a) and another one with high CV (b) in tumour volume. The median survival of patients with CV in tumour volume below 1.8 was 25.0 months and that above 1.8 was 16.1 months (Fig. 3).

Table 2
Correlation between clinicopathological factors and overall survival after hepatectomy for multiple colorectal hepatic metastases

	No. of patients	Median survival (mo)	*P*
Primary colorectal lesion			
Location			
Colon	31	23.4	0.63
Rectum	19	18.5	
Stage (TNM classification)			
I, II	10	20.4	0.44
III, IV	40	22.7	
Lymph node metastasis			
Absent	18	23.4	0.82
Present	32	19.7	
Histological type of adenocarcinoma			
Well or moderately differentiated	46	23.5	0.08
Poorly differentiated and others	4	12.5	
Hepatic metastases			
Number of tumours			
<5	20	21.1	0.61
≥5	30	23.4	
Maximum size of the tumour (cm)			
<5	40	23.5	0.02
≥5	10	15.9	
Distribution of metastases			
Unilobar	12	21.1	0.60
Bilobar	38	23.4	
Microscopic surgical margin			
Negative	39	23.4	0.95
Positive	11	21.3	
CEA level before treatment (ng/ml)			
<20	27	24.6	0.01
≥20	23	17.5	
Tumour volume ratio* (%)			
<8	41	23.4	0.04
≥8	9	17.5	
Coefficient of variation† in tumour volume			
<1.8	42	25.0	<0.01
≥1.8	8	16.1	
Synchronous/Metachronous			
Synchronous	24	24.4	0.80
Metachronous	26	18.0	
Interval between colorectal resection and hepatectomy			
<1 year	39	24.6	0.91
≥1 year	11	12.1	
Adjuvant chemotherapy after hepatectomy			
Absent	41	23.5	0.61
Present	9	16.4	

CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Table 3
Multivariate analyses of factors affecting overall survival after hepatectomy for multiple colorectal hepatic metastases

	Hazard Ratio (95% C.I.)	*P*
Hepatic metastases		
CEA level before treatment (ng/ml)		
<20	reference	0.07
≥20	2.39 (0.93–6.16)	
Tumour volume ratio* (%)		
<8	reference	0.87
≥8	1.10 (0.36–3.39)	
Coefficient of variation† in tumour volume		
<1.8	reference	0.01
≥1.8	4.08 (1.33–12.5)	

C.I., confidence interval; CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Discussion

Several reports have described the efficacy of resection for MCHM. Bolton et al. analyzed clinical outcomes of 165 patients who underwent hepatic resection for colorectal metastases, and evaluated its efficacy and safety for patients with more than four and/or bilobar hepatic metastases.[6] The prognosis for such patients was almost equal to that of patients with fewer than four and unilobar hepatic metastases. Weber et al. reported that the 5-year survival rate after hepatic resection for 155 patients with four or more metastases was 23%, and twelve 5-year survivors were observed.[19] Minagawa et al. similarly reported a 32% 5-year survival of patients with four or more tumours.[13] In the present study, overall survival after hepatic resection for MCHM was 48% at 3 years and 43% at 5 years. Our results reconfirm that hepatic resection is beneficial for some patients with MCHM of colorectal cancer.

We found that a CV in tumour volume of above 1.8 was the only independent poor prognostic factor after resection of MCHM. Dispersion of tumour volume for each tumour is variable among patients. However, no previous study has attempted to quantify the dispersion of tumour volume or to evaluate its prognostic significance in colorectal hepatic metastases, and then we studied the association between the dispersion of tumour volume, quantified by CV, and survival after hepatectomy. Coefficient of variation is a statistical measure of the dispersion of data. It represents the ratio of the standard deviation to the mean, and is a useful statistic for comparing the degree of deviation from one

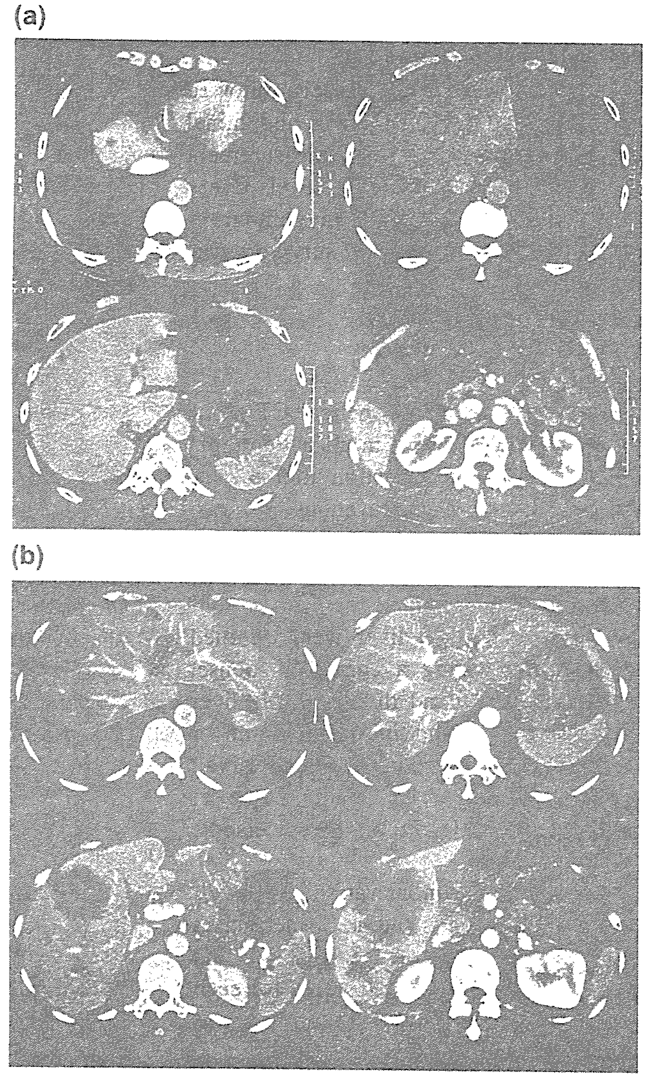

Figure 2. (a) A case of MCHM with low CV (=0.41) in tumour volume. (b) A case of MCHM with high CV (=3.20) in tumour volume.

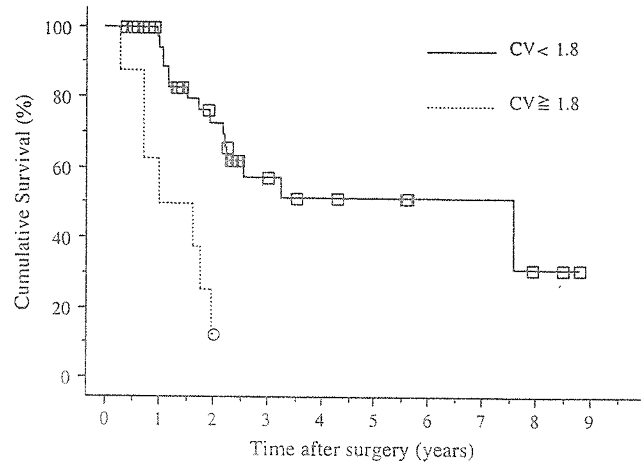

Figure 3. Cumulative survival curves after hepatic resection of MCHM according to CV in tumour volume. The median survival of patients with CV in tumour volume below 1.8 was 25.0 months and that above 1.8 was 16.1 months. Survival of patients with CV in tumour volume above 1.8 was poorer than that of patients with CV in tumour volume below 1.8 ($P < 0.01$).

data series to another, even if the means are drastically different from each other.[20,21] The mean tumour size varied widely among patients and CV was more useful than standard deviation in the present analyses.

The reason why high CV in tumour volume is strongly associated with independent poor prognosis after hepatic resection is obscure. However, a high CV may denote the coexistence of huge and tiny tumours. We propose two hypotheses to explain the association between high CV and poor prognosis. The first is that a high CV means the existence of a rapidly growing tumour; the high CV may result from the coexistence of tiny tumours growing at an ordinary rate and a huge tumour with an extremely aggressive nature and rapid growth. Another hypothesis is that high CV means a huge tumour with many intrahepatic metastases. Tiny tumours might have metastasized, not from the primary colorectal tumour, but from this huge hepatic tumour. Accordingly, a high CV might reflect progressive characteristics of MCHM.

In 8 patients with CV > 1.8, 6 suffered from severe hepatic recurrence after hepatic resection. In the remaining 2 patients, although lymph node recurrence was initially observed, hepatic recurrence with much tumour burden was recognized in the next few months. Then, severe hepatic recurrence could be a characteristic pattern of recurrence in patients with CV > 1.8. High CV might suggest extensive micro-metastases in the remnant liver.

Node-positive primary tumour,[4,22,23] serosal involvement of primary tumour,[22,23] stage of the primary tumour,[8,13] histological differentiation of primary tumour[22], a short disease-free interval from the primary tumour to metastasis,[4,11] extrahepatic disease at hepatectomy,[3,4,11,22,23] high CEA levels before hepatectomy,[4,5,8,10,22] large size of hepatic tumour,[4,8,23] the number of hepatic tumours,[4,5,8–13,22,23] bilobar distribution of hepatic tumour,[11] lymph node metastasis during hepatectomy,[3,11,13] an advanced age at hepatectomy,[8] and a positive margin of hepatectomy[4,5,8–11,22] have been reported as poor prognostic factors after resection of MCHM. However, the factors mentioned above were not found to be prognostic factors in this study. The difference between our results and those of other studies was partly due to difference of population. Patients of the present study consisted of only those with four or more metastatic lesions of colorectal cancer in the liver. Moreover, the difference might have resulted from the fact that CV in tumour volume, which had not been evaluated as a prognostic factor in other studies, affected patients' survival much more strongly than the aforementioned factors did in the present study.

In our study, the median survival of patients with CV in tumour volume above 1.8 was only 16 months and no 2-year survivors were found. Results of the present study lead us to conclude that hepatic resection is not